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(71) Applicants: INSTITUT PASTEUR [FR/FR]; 25-28, rue du Dr. Roux, F-75724 Paris Cedex 15 (FR). CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE [FR/FR]; 15, quai Anatole France, F-75008 Paris (FR).

(72) Inventors: CHASSAGNE, Jacques ; 3, rue de Leyrat, F-63670 Le Cendre (FR). VERRELLE, Pierre ; Rue Guyot-Dessaigne, F-63730 Plauzat (FR). KLATZMANN, David ; 84, quai de Jemmapes, F-75010 Paris (FR). MONTAGNIER, Luc ; 21, rue de Malabry, F-92350 Le Plessis Robinson (FR). DIONET, Claude ; 27, La Rivière, F-63670 Le Cendre (FR). GLUCKMAN, Jean-Claude ; 70, bld. de Port Royal, F-75005 Paris (FR).

(74) Agents: GUTMANN, Ernest et al.; 67, bd. Haussmann, F-75008 Paris (FR).

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(54) Title: MONOCLONAL ANTIBODIES AGAINST CORE PROTEINS OF LYMPHADENOPATHY-ASSOCIATED-VIRUSES

(57) Abstract

Monoclonal antibodies which recognize core proteins of lymphadenopathy-associated-viruses (LAV) and the hybridomas which secrete them. Monoclonal antibodies which recognize LAV p13, p18, p25 and p55 proteins are disclosed. Said monoclonal antibodies are useful in detecting the corresponding proteins or polypeptides in mixtures which contain them. When said antibodies are immobilized on an insoluble support, they can be used for the purification of the corresponding polypeptides from mixtures which contain them.

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Monoclonal antibodies against core proteins of lymphadenopathy-associated-viruses.

The invention relates to monoclonal antibodies which recognize polypeptides, whether glycosylated or not, encoded by genomic RNA of lymphadenopathy-associated virus (LAV), or cloned DNA derived therefore, to the hyridomas secreting said antibodies and to a process for their preparation and finally to their uses.

A method for cloning such DNA sequences has already been disclosed in British Patent Application Nr. 84 23659 filed on September 19, 1984, in the European Patent Application Nr. 85 401799 filed on September 17, 1985 and in the International Patent Application PCT/EP/85 00487 filed on September 18, 1985. Reference is hereafter also made to these applications as concerns subject matter in common with the further improvements to the invention disclosed herein.

The present application will also refer herein to the contents of the International application filed on October 18, 1985 PCT/EP 85 00548 on behalf of INSTITUT PASTEUR and the CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE. It is understood that the contents of the two preceding applications are entirely incorporated herein by reference.

More particularly the molecular cloning of both cDNA and integrated proviral forms of LAV have been reported. The recombinant phage clones were isolated from a genomic library of LAV-infected human T-lymphocytes DNA partially digested by HindIII. The insert of recombinant phage λJ19 was generated by HindIII cleavage within the R element of the long terminal repeat (LTR). Thus each extremity of the insert contains one part of the LTR. The

possibility of clustered HindIII sites within R has been eliminated by sequencing part of a LAV cDNA clone, pLAV 75, corresponding to this region. Thus the total sequence information of the LAV genome can be derivated from the λJ19 clone.

Using the M13 "shotgun" cloning and dideoxy chain termination method (Sanger et al., 1977), the nucleotide sequence of the λJ19 insert has been determined. The reconstructed viral genome with two copies of the R sequence is 9193 nucleotides long. The numbering system starts at the cap site of virion RNA. The entire sequence is shown in figs 1a-1e of the International application, also enclosed herewith.

The present invention aims at providing for the more accurate identification of significant LAV proteins or glycoproteins and also at providing monoclonal antibodies against proteins and polypeptides carrying significant immunogenic sites or epitopes of the LAV virus proteins or glycoproteins.

The invention is more particularly concerned with monoclonal antibodies which recognize LAV core proteins or fragments thereof, particularly the p13, p18, p 25 and p55 proteins.

The invention is thus more particularly concerned with and relates to monoclonal antibodies which recognize respectively :

- a p55 protein deemed to be encoded by the DNA sequence, extending from about nucleotide 336 up to about nucleotide 1650 of the LAVcDNA, which p55 protein is considered to contain aminoacid sequences corresponding to those of the core proteins p18 and p25 of the LAV virus ;
- a p25 protein, deemed to be encoded by the DNA sequence, extending from about nucleotide 732 up to about nucleotide 1300 of LAVcDNA ;

- a p13 protein, deemed to be encoded by the DNA sequence, extending from about nucleotide 1371 to about nucleotide 1650 ;
- a p18 protein, deemed to be encoded by the DNA sequence, extending from about nucleotide 336 up to about nucleotide 611.

More particularly the invention relates to monoclonal antibodies recognizing polypeptides having peptidic sequences identical or equivalent to those encoded by the DNA sequences extending approximately between the following nucleotide positions :

- 336 to 1650 (p55)
- 336 to 611 (p18)
- 1371 to 1650 (p13)
- 656 to 1300 (p25).

It should be mentioned that the p13, p18 and p25 all appear to derive from a same precursor, i.e. p55.

More particularly the invention concerns the monoclonal antibodies produced by the hybridomas deposited on October 24, 1984 at the "Collection Nationale des Cultures de Micro-organismes" or, under the abbreviated form "CNCM", under the numbers which follow :

LAV-A1 (p18) ..... n° I-355
LAV-B1 (p25) ..... n° I-356
LAV-C1 (p25) ..... n° I-357
LAV-D1 (membrane) .. n° I-358
LAV-E1 (p25) ..... n° I-359
LAV-F1 (p13) ..... n° I-360.

The designations used for identifying the hybridomas correspond to the purified peptides obtained by standard purification procedures starting from lysates of LAV virus, which peptides were initially used for immunizing the animals from which the splenic cells used for the production of the corresponding hybridomas were

obtained. Purified peptides for use in the production of said monoclonal antibodies can also be obtained by immunizing animals with the corresponding purified expression products of the DNA recombinants disclosed in the abovementioned PCT application and European application. The general procedure for making said hybridomas will be described later.

A general procedure used for the production of each of the above said monoclonal antibodies will be described hereafter.

Immunisation of mice

Groupes of 6-8 week old Balb/c mice were used. The different groups received the different proteins mentioned hereabove respectively. The immunization protocols, identical in all groups, comprised injections three times by the intraperitoneal route, then once by the intravenous route, each time of 10 µg of the antigenic preparation in the presence of Freund complete adjuvant at day 0, and of incomplete Freund adjuvant at day 14 without adjuvant at days 28 and 42.

Fusion and culture of the hybrids

the azaguanine-resistant and non secretor variant 6.53 of myeloma P3 X 63 Ag8, which itself originated from the MPOC-21 cell line was used. The fusion with the splenocytes of the immunized mice was performed in the presence of polyethylene-glycol 4000, according to the technique of FASEKAS DE ST-GROTH and SCHEIDEGGER at day 45. The selection of the hybrides in RPMI 16-40 "HAT" medium was carried out according to the same culture technique in plates comprising 24 wells (Costar).

The hybridomas which produced the specific antibodies were then cloned in plates comprising 96 wells respectively, in the presence of a feeder layer of syngenic thymocytes. The secreting clones selected were then

expanded in plates comprising 24 wells respectively, still in the presence of thymocytes. When confluence appeared in one of the wells, the clone was intraperitoneally injected to BALB/c mice which had received 8 days earlier an injection of Pristane and/or maintained in liquid culture.

Detection of the anti-LAV antibodies

Five different techniques have permitted the characterisation of clones producing the antibodies of desired specificity. In a first step, the hybrids secreting the desired antibodies were detected by an ELISA assay that revealed the mice immunoglobulins in the supernatant. Starting from this first selection, the supernatants which contained antibodies oriented against the viral constituents sought were screened by means of an ELISA assay or by an immunogluorescence assay on human cells that produced the virus. Finally the supernatants were analyzed by radio-immunoprecipitation of virus labelled with ^{35}S-cysteine and by the Western-Blot technique on a viral preparation whereby the specificities of the anti-LAV antibodies were determined.

RESULTS

The cells obtained, starting from different fusions were then cultivated in 648 wells. The microscopic examination has shown that most of these wells contained a single hybrid clone capable of growing in the "HAT" selective medium. More than 50 % of the clones produced antibodies that provided a positive response in the antivirus ELISA assay. The most representative fusions were tested by the Western-Blot technique and several hybridomas of each group were sub-cloned, taking into account their specificity, their reactivity in the antivirus ELISA assay and their development rate in cultures. Hybrids were retained which produced antibodies which recognized more specifically the proteins or polypeptides which had been

used initially for immunizing the mice. All sub-clones obtained were shown to secrete antibodies which after expression, were injected in syngenic mice. The analysis of antibody specificities in the different ascites liquids obtained confirmed the specificities of the antibodies formed in each of the ascites with respect to the corresponding proteins.

The hybridomas which have been deposited at the CNCM and which were identified above are representative of the hybridomas that can be obtained using the above proteins. They form part of the invention too.

The monoclonal antibodies obtained can themselves be brought into play for purifying porteins or polypeptides which have in common an antigenic site with the proteins initially used for producing the hybridomas. The invention thus also relates to the purification processes per se. Such processes are advantageously used for the treatment of lysates of LAV, of infected T lymphocytes or of any other cells capable of producing LAV or an analogous virus. This process can also be applied to the identification of the proteins produced by cells which have been genetically engineered with recombinant DNAs as defined above and containing a DNA sequence encoding the relevant epitope. The monoclonal antibodies used in said process are advantageously immobilized on a solid support, for instance one suitable for affinity chromatography operations, such as a tri-dimensional cross-linked agarose lattice, commercialized under the trademark SEPHAROSE by the Swedish Company PHARMACIA A.G., for instance by the cyanogene bromide method.

The process of the invention thus comprises the step including contacting the solution containing said polypeptide with an affinity column carrying said monoclonal antibodies in order to selectively retain said

polypeptides, then recovering the polypeptide upon dissociation of the antigen-antibody complex by means of an appropriate buffer, for instance a salt solution of appropriate ionic strength, for instance at pH 2-4. A suitable salt for constituting such buffers is formed of ammonium acetate.

Having isolated such polypeptide it will immediately appear that the same monoclonal antibodies can be further used for the study fo fragments obtained from the corresponding polypeptide likely to contain the relevant epitope, said fragments having been obtained from the larger polypeptide, for instance by cleavage of the latter by enzymes capable of fragmenting polypeptides or proteins. By way of examples of such enzymes, one may mention the enzyme of Staphylococcus aureus V 8, alpha-chymotrypsin, the mouse sub-maxillary gland protease commercialized by the BOEHRINGER Company, the collagenase Vibrio alginolyticus chemovar iophagus , which recognizes specifically Gly-Pro and Gly-Ala dipeptides, etc..

the monoclonal antibody produced by the hybridoma deposited at the CNCM under Nr. I-355 is of particular significance. More particularly the monoclonal antibodies recognize both p18 and p55. Consequently it follows that the epitope more significantly recognized by said antibody remains unmodified when p55 (precursor of p18 and p25) is cleaved into its different components.

Thus this antibody is of particular interest for purifying both p18 and p55. The other components included in p55, particularly p25 can then be purified starting from the purified p55. It has been further found that said antibody is capable of recognizing the LAV virus in compositions containing same. It can be hypothesized that p18 behaves accordingly as a transmembranous protein, which is at least particularly exposed through the virus envelope

and which is further expressed by the cells.

This antibody is thus of particular interest for
- the detection of viral particles in a biological sample, particularly a serum obtained from patients to be diagnosed for AIDS or LAS,
- the detection of infected lymphocytes,
- the detection in a biological sample as mentioned above or in a culture of infected lymphocytes,
- the treatment by the antibody of cells which express the virus.

The invention further relates
- to any other monoclonal antibody which recognizes any of the epitopes more specifically recognized by the monoclonal antibodies secreted by the hybridomas which have been deposited at the CNCM and, accordingly,
- to the hybridomas which secrete said other monoclonal antibodies.

CLAIMS

1 - Monoclonal antibodies which recognize a core protein of the lymphadenopathy associated-virus (LAV).

2 - The monoclonal antibodies of claim 1 which recognize a p13 protein of LAV.

3 - The monoclonal antibodies of claim 1 which recognize a p18 protein of LAV.

4 - The monoclonal antibodies of claim 1 which recognize a p25 protein of LAV.

5 - The monoclonal antibodies of claim 1 which recognize a p55 protein of LAV.

6 - The monoclonal antibodies of claim 1 which recognize both a p13 protein and a p25 protein of LAV.

7 - A monoclonal antibody according to claim 1 selected from the group of the monoclonal antibodies which are secreted by the hybridomas deposited at the CNCM under numbers I-355, I-356, I-357, I-358, I-359 and I-360 or any monoclonal antibody recognizing the same epitope as that recognized by a monoclonal antibody produced by any of the above-mentioned hybromas.

8 - The hybridomas which secrete the monoclonal antibodies of any of claims 1 to 7.

9 - The use of a monoclonal antibody according to any of claims 1 to 7 for the in in vitro detection of the corresponding polypeptides in a biological sample or of the corresponding expression products on LAV-infected lymphocytes.

10 - A method for the purification of a polypeptide contained in solubilized form in a biological sample, which polypeptide contains an epitope recognized by one of the monoclonal antibodies according to any of claims 1 to 7, wherein said method comprises contacting said biological medium with the corresponding monoclonal antibody affixed to or immobilized on an insolubilized support for

causing the fixation of said polypeptide on said immobilized monoclonal antibody, whereby a polypeptide-antibody complex is formed, separating the non fixed polypeptides and recovering said fixed antibody by the dissociation of said polypeptide-antibody complex.

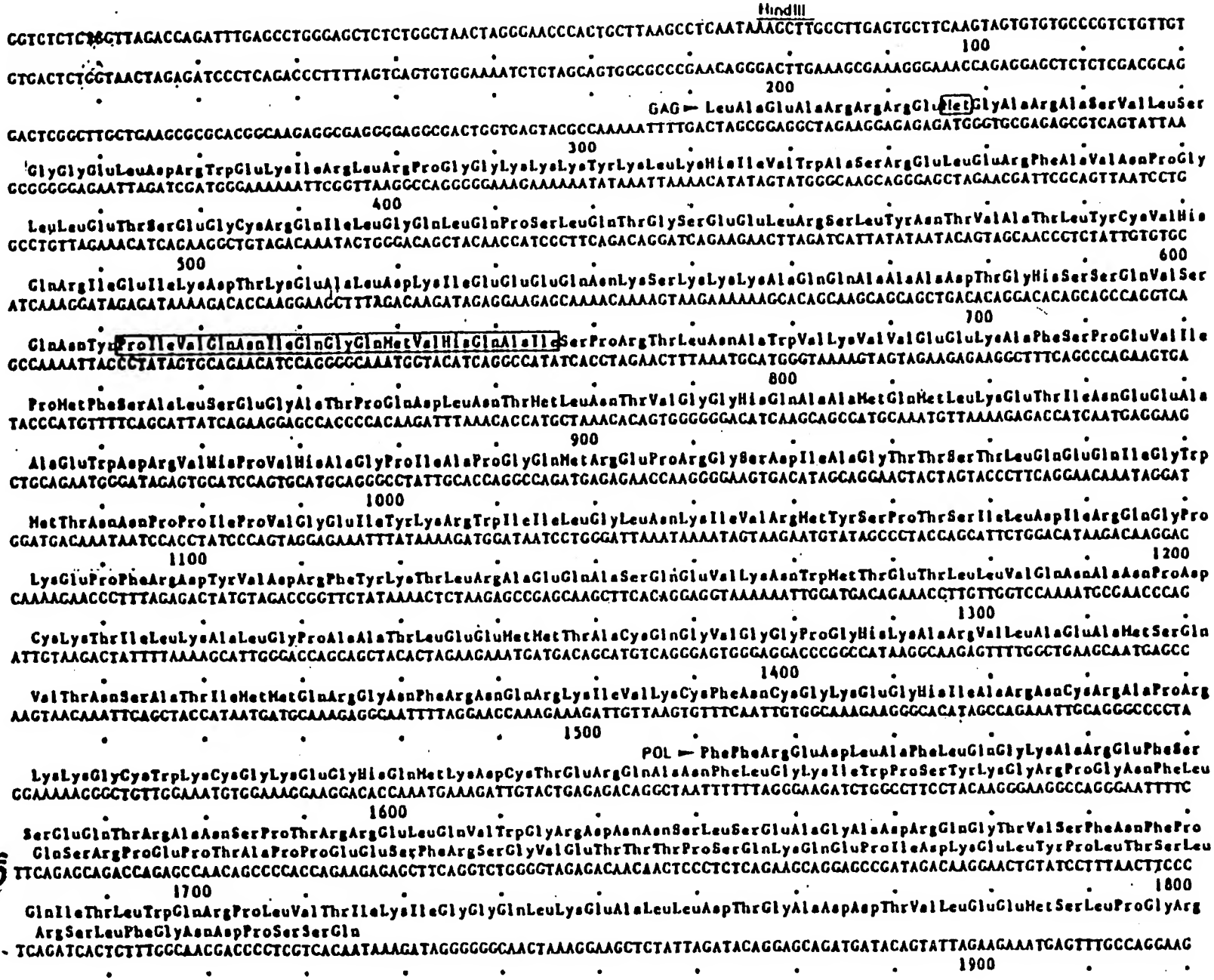
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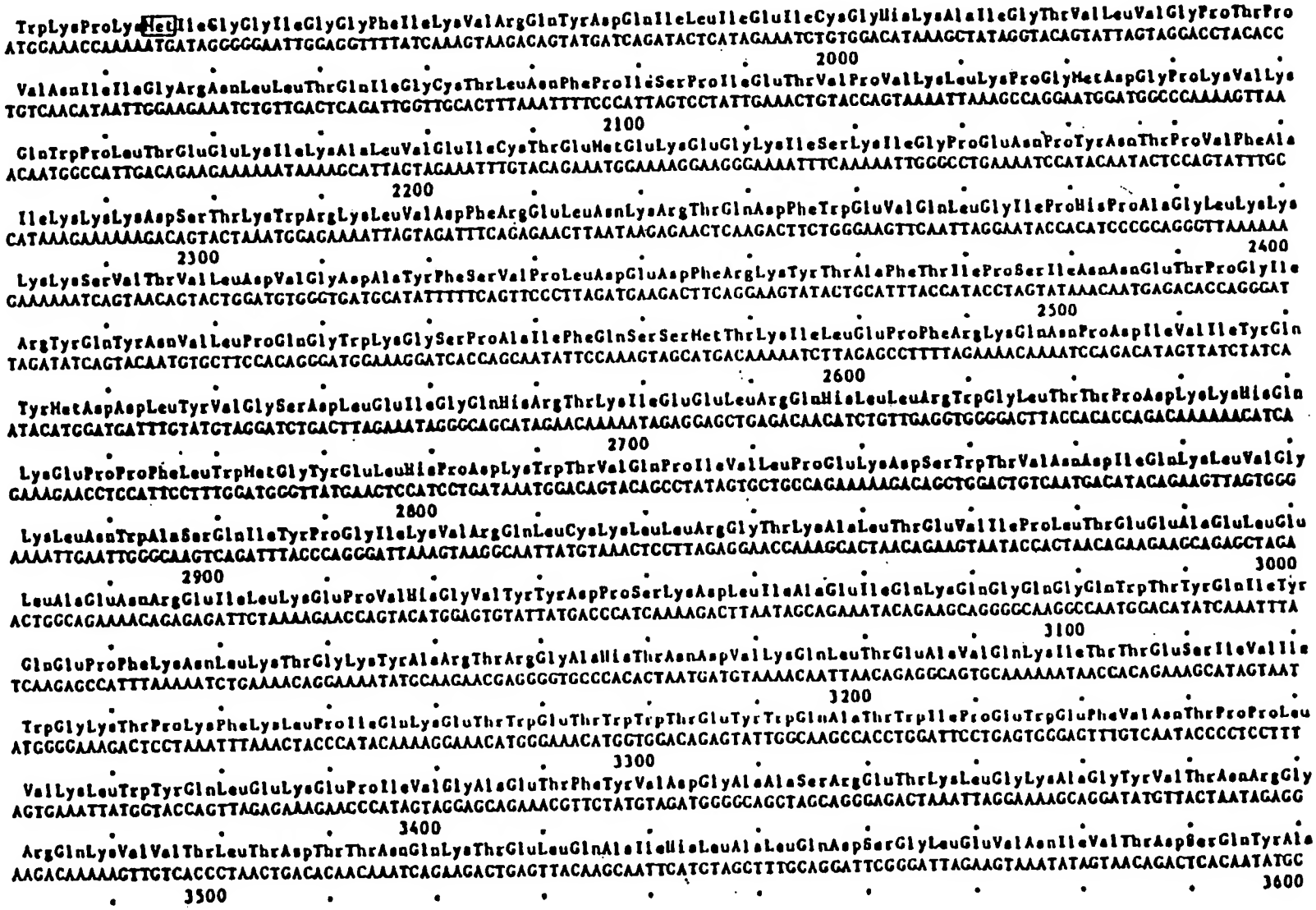
FIG. 1a

FIG. 1b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  AspCysPheSerAspSerAlaIleArgLysAlaLeuLeuGlyHisIleValSerProArgCysGluTyrGlnAlaGlyHisAsnLysValGlySerLeuGlnTyrLeuAlaLeuAlaAla
TTGACTGTTTTTCAGACTCTGCTATAAGAAAGGCCTTATTAGGACATATAGTTAGCCCTAGGTGTGAATATCAAGCAGGACATAACAAGGTAGGATCTCTACAATACTTGGCACTAGCAG
                                                                  5000
  LeuIleThrProLysLysIleLysProProLeuProSerValThrLysLeuThrGluAspArgTrpAsnLysProGlnLysThrLysGlyHisArgGlySerHisThrMetAsnGlyHis
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                                                5200
CATAATAAGAATTCTGCAACAACTGCTGTTTATCCATTTCAGAATTGGGTGTCGACATAGCAGAATAGGCGTTACTCAACAGAGGAGAGCAAGAAATGGAGCCAGTAGATCCTAGACTAG
                                                5300                                                                5400
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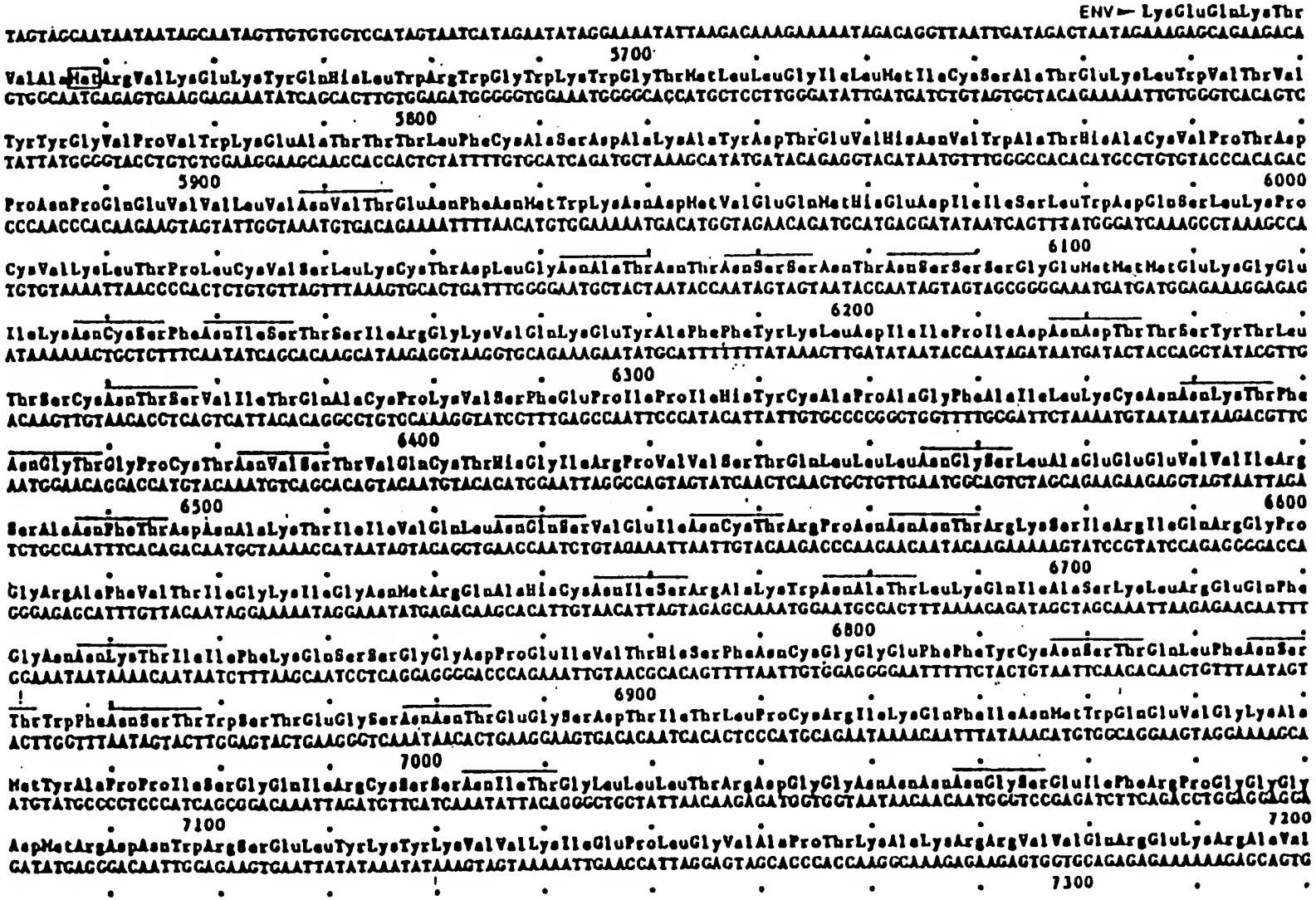
FIG. 1c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5900
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6100
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6200
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6300
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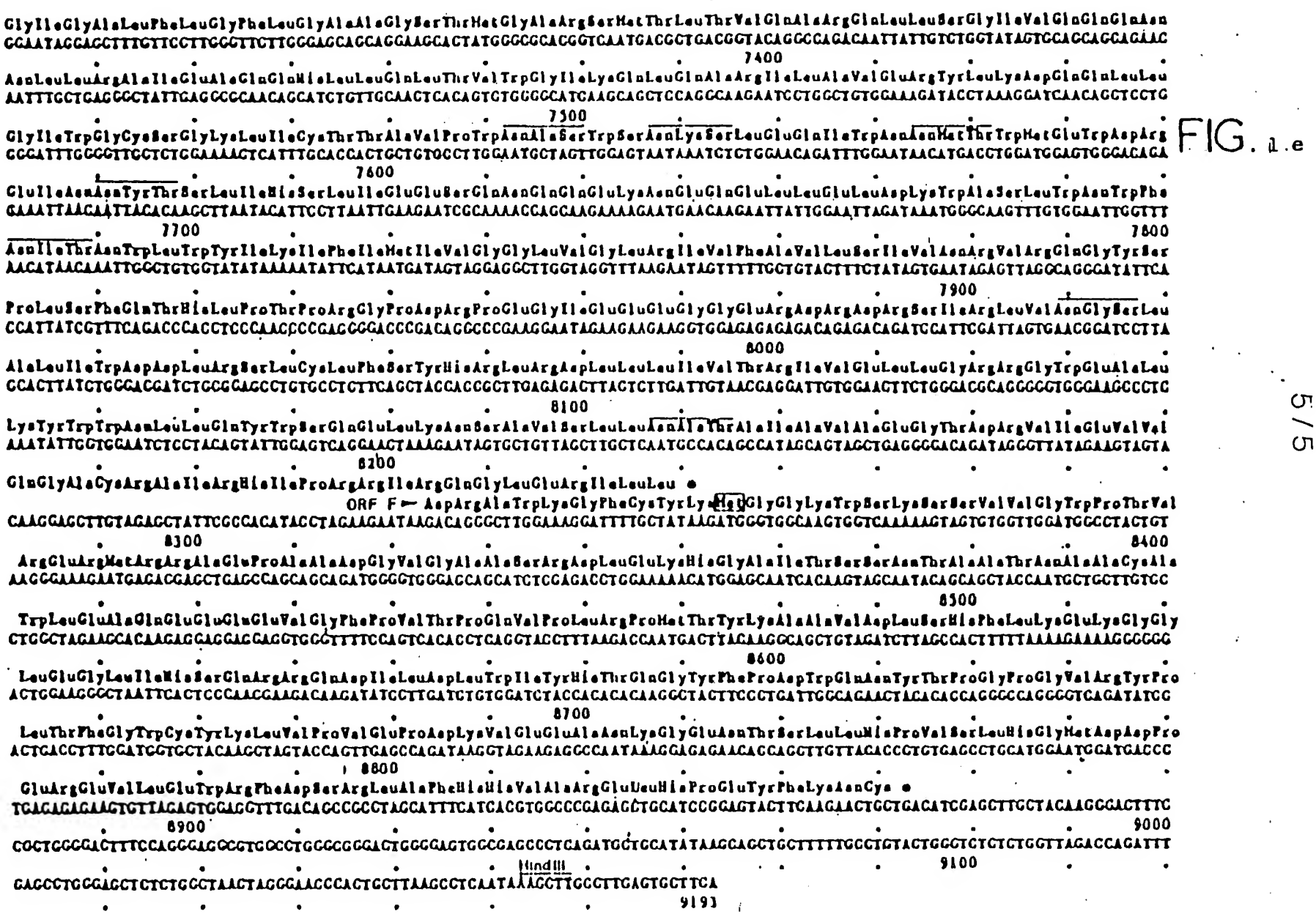
7300

FIG. 1a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7700
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7800
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8100
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8800
8900
9000
HindIII
9100
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FIG. 1.e

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 86/00018

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 K 15/00; C 12 P 21/00; C 12 N 5/00; G 01 N 33/569; G 01 N 33/577; C 07 K 3/18 // C 12 N 15/00 ./.

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 12 P A 61 K G 01 N

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,P	EP, A, 0138667 (INSTITUT PASTEUR) 24 April 1985, see page 7, line 34 - page 8, line 17; page 9, lines 6-11,18-25; page 10, lines 23-32; page 11, line 11 - page 12, line 7; page 23, lines 13-21 and line 29 - page 24, line 5; claims 1,5-7 --	1,4,7,8
X,P	Proc. Natl. Acad. Sci. USA, volume 82, August 1985 F. Di Marzo Veronese et al.:"Monoclonal antibodies specific for p24, the major core protein of human T-cell leukemia virus type III", pages 5199-5202, see page 5199, left-hand column, lines 11-16; right-hand column, lines 9-13; page 5200, left-hand column, lines 35-42; right-hand column, line 10 - page 5201, left-hand column, line 1; page 5201, left-hand column, lines 8-16,23-36 --	1,4,7,8
X,P	Biological Abstracts/Reviews, Reports, Meetings, 1985 F.V. Dimarzo et al.:"Monoclonal anti-	./.

* Special categories of cited documents: [10]

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15th April 1986	22 MAI 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 86/00018

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: (C 12 P 21/00; C 12 R 1:91)

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC[4]	

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
	bodies specific to human T cell leukemia virus III gag proteins", , see title and terms	1-8
	--	
A	Science, volume 225, 6 July 1984 P.M. Feorino et al.:"Lymphadenopathy associated virus infection of a blood donor-recipient pair with acquired immuno-deficiency syndrome", pages 69-72, see page 69, abstract, lines 1-3,10-12; left-hand column, lines 1-13; middle column, lines 6-10; page 70, left-hand column lines 6-11,23-26; right-hand column, lines 34-54; page 72, left-hand column, lines 9-14	1,4
	--	
A	Journal of Experimental Medicine, volume 159, April 1984 T.J. Palker et al.:"Monoclonal antibodies against human T cell leukemia-lymphoma virus (HTLV) p24 internal core protein", pages 1117-1131, see page 1117, lines 4-12,16-18; page 1118, lines 3-11; page 1129, lines 25-28,31-35	1-9

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
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International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 86/00018 (SA 11930)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/05/86

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0138667	24/04/85	AU-A-	3307884	21/03/85
		JP-A-	60067859	18/04/85